
OAR Box 1194

Prepped by Candice Davis

Document Number:

30) IV-F-2

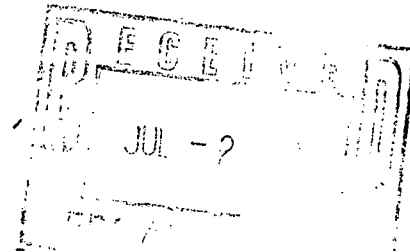
Docket Number:

A-90-16

A-90-16
IV-F-2

June 19, 1990

AIR DOCKET (LE-131)
US Environmental Protection Agency
Room M-1500
401 M Street SW
Washington, D.C. 20460



COMMENTS OF THE ENVIRONMENTAL DEFENSE FUND ON THE WAIVER
APPLICATION BY ETHYL CORPORATION FOR METHYCYCLOPENTADIENYL
MANGANESE TRICARBONYL (MMT) AS A GASOLINE ADDITIVE

The Environmental Defense Fund submits these comments on the application by the Ethyl Corporation to add MMT, an organomanganese compound, to gasoline as an octane enhancer. EDF is a national, nonprofit, environmental research and advocacy organization with over 100,000 members throughout the United States. These comments are prepared by Ellen K. Silbergeld, Ph.D., Senior Scientist and Director of the Toxic Chemicals Program. EDF intends to submit an expanded version of these comments before the close of the public comment period; this document is for purposes of the public hearing.

Over the past decade, I have served on several EPA committees charged with assessing environmental fate and transport, exposure, and health impacts of another organometal gasoline additive also manufactured by Ethyl tetraethyl lead. In addition, I have provided comments on request to the governments of Canada, Bermuda, Thailand, and Mexico on the topic of lead additives to gasoline. Since receiving my Ph.D. from Johns Hopkins in 1972, I have actively conducted basic and clinical research on the effects of low level chronic exposure to both lead and manganese. While I was at NIH, I provided expert opinion via the Director of NINCDS to the government of Bolivia on the potential effects of manganese in drinking water. More recently, I was a peer reviewer of EPA's most recent health assessment of manganese. I also reviewed the recent Health Effects Institute paper on the health effects of manganese as an additive to gasoline.

Earlier this month, I met with two representatives of Ethyl, Dr. Gary Ter Haar and Dr. Donald Lynam, at their request, to hear their position in support of Ethyl's application to use MMT in unleaded gasoline. I am aware of the arguments and data upon which Ethyl's application is based.

EDF strongly opposes granting this waiver application. The Clean Air Act provides that EPA "may" grant a waiver allowing the use of manganese as a fuel additive upon determining that the additive will not impair emissions control devices such as the catalytic converter. Regardless of the effects of MMT on emissions control, there is no dispute that manganese is neurotoxic to humans. On this basis, EPA should deny this waiver, particularly since Ethyl has failed yet again to provide relevant or convincing evidence that use of MMT will not affect

human health. EDF believes that it would be an abrogation of EPA's clear responsibility under the Clean Air Act to protect human health, to do otherwise.

It is rare that an opportunity arises to apply the clear lessons of the past 50 years' experience with a very similar application. To disregard these lessons by approving the widespread and inherently dispersive use of another neurotoxic metal would be to invite repetition of the public health catastrophe associated with the use of lead as a gasoline additive from 1925 to the present. The 1988 ATSDR report to Congress on childhood lead poisoning documents that lead toxicity is an epidemic in the United States. Even after considerable reductions have been imposed on the use of lead in gasoline -- after prolonged debate and litigation, it should be noted -- we are only now confronting the extraordinarily difficult challenge of cleaning up the residues of lead fallout from city playgrounds, school yards, and backyards around America. Dr. Katherine Farrell and Dr. Boon Lim, of the Maryland Department of Environment, are currently conducting research, sponsored by EPA, on the significance of soil lead as a source of exposure for urban children; a recent report from the California Department of Health Services already demonstrates the quantitative relationship between soil lead and childrens' blood lead levels.

This is an experience we cannot afford to repeat. The parallels between Ethyl's proposal in 1990, to use manganese, and its proposal in 1925, to use lead, are chilling. In both cases, the exclusive basis for this application is its purported effect on emissions of hydrocarbons and NOx from cars. No data were or are submitted on the potential cumulative health effects of massive inputs of a toxic metal into the environment, its deposition into surface dusts and soils, and its longerm fate and exposure pathways to humans. In 1925, Ethyl argued that the amounts of lead to be added to gasoline were of negligible importance, and that lead was only toxic at the high doses encountered in certain industrial settings. In 1990, Ethyl argues that the releases of manganese to the environment will be insignificant and that manganese is only toxic at high doses in industrial settings. In both cases, Ethyl has suggested that acceptance of its additive is of critical importance to the nation (see generally Rosner and Markowitz (1983) [attached] for the historical perspective on Ethyl's campaign to secure acceptance of tetraethyllead).

In 1925, over the prophetic objections of Dr. A. Hamilton and Y. Henderson, the U.S. Public Health Service acquiesced in approving Ethyl's application despite the absence of any data the impact of lead additives on environmental concentrations of lead or the health effects of low level, chronic lead exposure, particularly in children. The PHS urged that these and other issues be considered in a reevaluation to be conducted at some later point; this reevaluation did not commence until 1977. By then, millions of tons of lead had been spread throughout America.

In 1990, amazingly, Ethyl finds it unnecessary to do anything more than it did in 1925. Wholly inadequate data are presented to indicate that adding manganese to gasoline does not change concentrations of manganese in ambient air over the short term in some selected Canadian cities. Ethyl does not cite a recent study from California indicating that increases in airborne manganese in air samples are related to additions of manganese to gasoline already permitted by EPA (see Davis, et al, 1988; references attached). No in-depth discussion of the health effects of manganese is presented, nor -- more importantly -- is there a discussion of the critical datagaps on manganese toxicity that must be filled before any decision can be approved that would result in tons of manganese released into the environment (see attached bibliography).

EPA must assert its leadership role in 1990 to defend the preventive imperative of its mandate to protect human health and the environment. What is at stake is not the health of emission control devices in automobiles but the health of humans. This waiver cannot be approved until the applicant provides substantive information on the cumulative impacts of manganese additives on environmental quality (not solely ambient air concentrations) and convincing evidence that such impacts will not adversely affect the health of any segment of the human population over the longterm.

In making this case, Ethyl must demonstrate that the likely experience with manganese will not resemble that with lead. This demonstration will be difficult. Both lead and manganese are elements and as such will not degrade or quickly disappear from stable environmental compartments, such as soils, dusts, and sediments. Patterns of use will result in relative enrichment in urban, densely populated areas with high levels of vehicular traffic and residential patterns such that persons are in close contact with the areas most heavily impacted by fallout from vehicle emissions. While the proposed per gallon usage of manganese is less than the usage of lead in gasoline at its peak prior to regulation in 1978, the vastly increased amount of gasoline consumed and number of vehicle miles driven in the U.S. in 1990 as compared to 1925 will ensure that the rate of contamination of our environment from this source will be comparable.

Both lead and manganese are neurotoxic metals. While the data on manganese is relatively sparse (compared to lead -- but we have not yet conducted a massive human experiment with manganese), the hazard identification of manganese as a neurotoxin and lung toxin is clear (see generally EPA's HAD on manganese and attached bibliography). Manganese, like lead, is a cumulative toxin in that both its absorption and retention as well as its toxicity increase with time. At present, there are insufficient data on the low level, chronic sequelae of manganese exposure -- similar to the case for lead in 1925 as noted above. There are no data on the effects of manganese on the ageing

brain, although it has been suggested that the nature of manganese-induced pathophysiology -- damage to the nigrostriatal system -- is such that interaction with normal cell loss during senescence would be expected. The potential for selective susceptibility to manganese in the aged must be of great concern as the U.S. population ages. Studies on the population of Groote Eylandt disease by Cawte (which I was one of the first persons to review over ten years ago) suggest that there may also be fetal and early developmental effects of manganese. The possibility that iron deficiency may potentiate manganese toxicity is of considerable concern, given the prevalence of iron deficiency in the U.S. (see NHANES II data).

The mechanisms by which manganese damages neural tissue (particularly catecholaminergic pathways) are unknown, so that we cannot propose an overall dose response relationship or rational basis for risk assessment. There are inadequate studies on the immunotoxic effects of MMT or manganese. The toxicokinetics of low dose manganese exposure are not known; the observations of apparent decreases in brain manganese concentrations with prolonged exposure are at relatively high exposures and may reflect a pathological effect (e.g., loss of normal Mn binding sites, such as enzymes or other proteins) rather than a protective effect. These rather odd toxicokinetics have not been replicated in primates. Moreover, as the study by Yamada et al indicates, the expression of severe akinetic and neuropsychiatric symptoms were not associated with increased concentrations of manganese in brain, further indicating that the mechanisms as well as the toxicokinetics of manganese are not well understood. No defined biological markers for manganese exposure in humans have been validated, so that interpretation of epidemiological studies is limited.

In summary both what we know and do not know at present about the likely toxic effects of adding manganese in large total amounts to the environment must persuade EPA to reject this application. We know that manganese at high dose is a demonstrated human neurotoxin, with persistent and irreversible pathological effects on brain structure and resulting severe impairments in movement and mental state. We do not know what the longterm, chronic, low dose consequences of human exposure to manganese are. We do not know a "safe" level of manganese exposure, particularly for those subgroups that may be at increased risk for neurotoxicity (the young and the aged). We do not know if manganese is carcinogenic, although there is evidence that it can break DNA.

With respect to exposure assessment in contrast, we know great deal, based upon our tragic experience with lead, about likely cumulative impacts of such a use upon human exposure to manganese. We know that the gradual contamination of the environment by this additive will not be readily reversed.

that manganese will accumulate in specific parts of the environment, many of which are subject to intensive human interaction (urban dusts and soils). We know that manganese in air and in surface dusts and soils will be present directly to humans as a source of exposure.

Ethyl has chosen to focus in its application on the purported efficacy of manganese additives to reduce certain pollutant emissions from vehicles. In a well mounted publicity campaign over the past week, Ethyl has sought to harness concerns over the impacts of these air pollutants on global and local air quality as justification. Ethyl has selectively cited bits of data in support of its contention that use of MMT will not increase manganese concentrations in air in cities. Ethyl has provided no data on impacts of manganese additives on manganese concentrations in more stable postdeposition compartments, such as dusts and soils. Ethyl has provided no in depth review of the data and datagaps on manganese toxicity.

In 1925, Ethyl introduced its new product tetraethyllead as "a gift of God." It has taken us over 50 years to realize how diabolical this "gift" has proven to be. The reduction of lead in gasoline represents one of the most significant public health achievements of the EPA. I am proud to have participated in that victory. Now in 1990 Ethyl comes bearing yet another gift. To this offering, EPA must just say "No." The purported "benefits" of reducing climatic impacts cannot be achieved upon the rack of an epidemic of manganism. EDF urges rejection of this application and immediate suspension of all permitted use of manganese as a gasoline additive in the U.S.

A-90-16
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Search Strategy:

((MANGANESE[ALL] OR MN[ALL]) AND ((AIR[ALL] OR SOIL[ALL] OR SOILS[ALL] OR
LAND[ALL] OR GROUND[ALL]) AND (PETROL[ALL] OR PETROLEUM[ALL] OR (GAS[ALL] OR
GASOLINE[ALL]))

DOCUMENT 7 of 17:

AU: AUTHOR

Davis DW; Hsiao K; Ingels R; Shikiya J

TI: TITLE

Origins of manganese in air particulates in California.

SO: SOURCE

J. AIR POLLUT. CONTROL ASSOC.; vol. 38, no. 9, pp. 1152-1157; 1988

PY: PUBLICATION YEAR

1988.

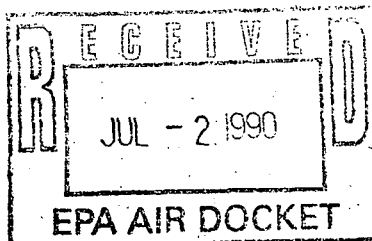
LA: LANGUAGE

English

AB: ABSTRACT

The proportions of manganese to other metals in samples of air-borne fine particles taken at some sites in California have increased greatly since the beginning of 1985. Here, data are presented which indicate that the addition of manganese to leaded gasoline is largely responsible for this increase. Concentrations of manganese, silicon, titanium, iron, lead and other elements in airborne particles were measured using energy-dispersive X-ray fluorescence analysis. Coefficients of correlation among levels of manganese, iron and lead measured at twenty sites in California were calculated. Levels of manganese and iron are generally highly correlated because of the presence of large amounts of these elements in the earth's crust. Levels of airborne manganese and lead at sites in Southern California are often highly correlated, suggesting a vehicular source of manganese.

ABSTRACT.



3F: NIOSH

T1: The Present Status Of Biological Effects Of Toxic Metals In The Environment: Lead, Cadmium, And Manganese

AU: Bhukia-GS; Singhal-RL

80: Canadian Journal of Physiology and Pharmacology, Vol. 62, No. 6, pages 1015-1031, 187 references, 1984

4B: Lead (7439921), cadmium (7440-39-9), and manganese (7439965) toxicities are reviewed. The sources of these metals and their presence in air, water, soil, and food is addressed. Experimental and epidemiological studies of exposure are reviewed. Emphasis has been placed on nervous system effects from

exposure to low concentrations. These metals appear to produce behavioral changes by altering the metabolism of brain neurotransmitters. Clinical and animal data show that lead and manganese are most toxic to the nervous system, while cadmium exerts adverse effects on the kidney and the male reproductive system. It is hypothesized that the metals exert their toxic effects by damaging biologic defenses that exist in the body to serve as protective mechanism against exogenous toxins. The importance of studying combined health effects of toxins is emphasized; humans are exposed simultaneously or successively to different physical, chemical, biological, and psychological factors, and other factors such as drug therapy, cigarette smoking, alcohol ingestion, and coexistent disease may influence individual susceptibility to these metals. Thus, at very low concentrations of a single metal, there may be severe impairment of absorption, distribution, receptor sites, or elimination of the toxic substance. Evidence shows that metals are capable of interacting with biologically important cellular systems at doses below those required to produce signs of overt toxicity. The authors conclude that it is essential to develop an appropriate model of metal toxicity that can serve as a predictive tool of toxic manifestations when encountered in combination with other metallotoxins.

AN: 00147720

38 of 82

SilverPlatter 1.6

TOXLINE (R) 1981 - 1987

16 of 82

EF: M102H

TI: Uptake, Distribution, And Behavioral Effects Of Inhalation Exposure To Manganese (MnO₂) In The Adult Mouse

PU: Morganti-JE; Lown-BA; Steinman-CH; DiAgostino-RB; Massaro-EJ

SD: NeuroToxicology, Vol. 6, No. 1, pages 1-16, 32 references, 1985

AB: The uptake, distribution, and behavioral effects of inhalation exposure to manganese (7439965) were studied in mice. Male ICR-Swiss-mice were exposed to manganese-dioxide (1313139) dust or filtered air 7 hours per day, 5 days per week for 16 to 32 weeks. Exposure concentrations were 49.1 milligrams per cubic meter (mg/m³) for the first 12 weeks and 85.3mg/m³ thereafter. Selected animals were observed for behavioral performance (ambulations and rearings in the open field, hole in the board exploration) and passive avoidance learning at weeks 16, 20, 24, 28, and 32. Body weights were measured. They were then killed and organs and tissues were taken and assayed for manganese. Tissue samples were examined for histopathological changes. Manganese exposed mice executed a significantly larger number of rearings in the open field and tended to show longer latencies to enter the open field. The exposed mice had higher body weights than control animals. Manganese exposed animals had significantly higher blood, liver, kidney, lung, cerebrum, cerebellum plus brain stem, and testes manganese concentrations than controls. With the exception of the liver, the manganese concentrations decreased with increasing exposure time after 20 weeks. Liver manganese concentrations increased with increasing exposure time. Manganese-dioxide exposure caused no detectable histopathological changes. The authors conclude that inhalation exposure to manganese has significant effects on mouse behavior, particularly those behaviors having an activity component; and causes a transient increase in tissue manganese concentrations. The decrease in tissue manganese concentrations observed in all organs except the liver would appear to have a protective function.

AN: 00149096

SilverPlatter 1.6

TOXLINE (R) 1981 - 1987

17 of 35

FF: NIOSH

TI: Preclinical Toxic Effects Of Manganese In Workers From A Mn Salts And Oxides Producing Plant

AU: Roels-H; Sarhan-MJ; Hanotiau-I; de-Fays-M; Genet-P; Bernard-A; Buchet-JP; Lauwerys-R

SO: Science of the Total Environment, Vol. 42, No. 1-2, pages 201-206, 18 references, 1985

AB: An epidemiological study of workers from a manganese (7439954) salts and oxides producing facility (SIC-2819) was conducted. The cohort consisted of 245 male subjects divided into 104 comparisons and 141 manganese exposed workers. Manganese-exposed workers were occupied at 11 workplaces. Total airborne manganese dust was monitored with personal samplers. Each subject was examined according to the following protocol: self-administered questionnaire; neurological examination; records of maximal expiratory flow volume curves, forced vital capacity (FVC), forced expiratory volume (FEV), peak expiratory flow rate (PEFR), and maximal expiratory flow rate (MEFR); psychomotor tests; and biological analyses. No relationship was found between manganese in blood and manganese in urine. There was no correlation between the concentrations of manganese in blood of each of the comparisons or exposed subjects and the current concentrations of manganese in air at each workplace. There was no correlation between duration of exposure and manganese in blood or manganese in urine. Analysis of the questionnaire revealed higher prevalences of cough, sputum, dyspnea, and acute bronchitis in the manganese exposed workers. Lung functions were mild and showed a slight decrease in MEFR at 50 and 75 percent of FVC in manganese exposed nonsmokers and a statistically significant difference in FVC, FEV, and PEFR between comparison smokers and manganese exposed smokers. Significant differences were found for fatigue, tinnitus, trembling of fingers, and increased irritability in manganese exposed workers. Manganese exposed workers performed less well during the psychomotor tests, and abnormal score values were higher for eye to hand coordination, hand steadiness, short term memory, and simple reaction time. The hematological data of manganese exposed workers did not differ from that for the comparison group. The authors suggest that preclinical perturbations may occur in subjects exposed to airborne manganese concentrations that are lower than concentrations actually tolerated

AN: 00147456

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Search Strategy:

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(NEUROLOG*[ALL] OR NEUROPATH*[ALL]) OR (NERVE[ALL] OR NERVES[ALL] OR
NERVOUS[ALL]))) AND MANGANESE[ALL]

DOCUMENT 47 of 85:

AU: AUTHOR

Donaldson J

TI: TITLE

The Physiopathologic Significance of Manganese in Brain: Its Relation to
Schizophrenia and Neurodegenerative Disorders

SO: SOURCE

NeuroToxicology, Vol. 8, No. 3, pages 451-462, 48 references, 1987

PY: PUBLICATION YEAR

1987

LA: LANGUAGE

English

AB: ABSTRACT

The physiopathology of elevated brain manganese (7439965) (Mn) was reviewed with the purpose of elucidating mechanisms of Mn neurotoxicity. Animal models of Mn pathology, case studies of Locura-manganica or manganese madness, the Groote Eylandt syndrome, chronic manganism, and manganese psychosis were discussed. Common observations included melanin loss, degeneration of the striatum or its components, and alterations in central dopaminergic receptors implying dopamine oxidation as a mechanism of Mn pathology. Hypotheses for Mn pathology reviewed included Mn induced enhancement of dopamine autooxidation, Mn catalyzed production of toxic catecholamines, Mn-self-oxidation and dismutation with resulting oxidative destruction of dopamine, and catecholamine oxidation by trivalent Mn. The role of zinc in protecting against Mn induced dopamine oxidation was attributed to the affinity of zinc ions for hydroxyl moieties and to the involvement of zinc in maintaining redox balance and membrane stability. The author suggests that tissue susceptibility to Mn toxic effects in the brain are related to the redox bioenergetic status of the various tissues and that other tissues with elevated levels of oxidative enzymes (oxidases, peroxides) such as testes, pancreatic-B cells, and macrophages would show similar sensitivity to Mn insult. ABSTRACT:

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Search Strategy:

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 NERVOUS[ALL])) AND MANGANESE[ALL]
 DOCUMENT 80 of 85:

AI: AUTHOR

Archibald FB; Tyree C

TI: TITLE

Manganese poisoning and the attack of trivalent manganese upon catecholamines.

SO: SOURCE

Arch Biochem Biophys; VOL 256, ISS 2, 1987, P638-50

PY: PUBLICATION YEAR

1987

LA: LANGUAGE

English

AB: ABSTRACT

Human manganese poisoning or manganism results in damage to the substantia nigra of the brain stem, a drop in the level of the inhibitory neurotransmitter dopamine, and symptoms resembling those of Parkinson's disease. Manganic (Mn³⁺) manganese ions were shown to be readily produced by O₂ in vitro and spontaneously under conditions obtainable in the human brain. Mn³⁺ as its pyrophosphate complex was shown to rapidly and efficiently carry out four-electron oxidations of dopamine, its precursor dopa (3,4-dihydroxyphenylalanine), and its biosynthetic products epinephrine and norepinephrine. Mn³⁺-pyrophosphate was shown to specifically attack dihydroxybenzene derivatives, but only those with adjacent hydroxyl groups. Further, the addition of Mn²⁺-pyrophosphate to a system containing a flux of O₂⁻ and dopamine greatly accelerated the oxidation of dopamine. The oxidation of dopamine by Mn³⁺ neither produced nor required O₂, and Mn³⁺ was far more efficient than Mn²⁺, Mn⁴⁺ (MnO₂), O₂⁻, or H₂O₂ in oxidizing the catecholamines. A higher oxidation state, Mn(OH)₃, formed spontaneously in an aqueous Mn(OH)₂ precipitate and slowly darkened, presumably being oxidized to MnO₂. Like reagent MnO₂, it weakly catalyzed dopamine oxidation. However, both MnO₂ preparations showed dramatically increased abilities to oxidize dopamine in the presence of pyrophosphate due to enhancement of the spontaneous formation of the Mn³⁺ complex. These results strongly suggest that the pathology of manganese neurotoxicity is dependent on the ease with which simple Mn³⁺ complexes are formed under physiological conditions and the efficiency with which they destroy catecholamines. ABSTRACT.

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Search Strategy:

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NERVOUS(ALL) AND MANGANESE(ALL)

DOCUMENT 88 of 88:

AU: AUTHOR

Milburn CJ

TI: TITLE

Manganese, malformations and motor disorders: Findings in a
manganese-exposed population.

SO: SOURCE

NEUROTOXICOLOGY.; vol. 8, no. 3, pp. 421-430; 1987

PY: PUBLICATION YEAR

1987.

LA: LANGUAGE

English

AB: ABSTRACT

This study attempts to further delineate aspects of the Groote Eylandt
syndrome, and by examining birth records and children, to explore the
possible effects of manganese during fetal and neonatal development. This
focus on the childhood population is in accord with both the clinical
expertise of the investigator and with experimental evidence which suggests
that manganese may be a particular hazard during fetal and neonatal
development. ABSTRACT.

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NERVOUS[ALL])) AND MANGANESE[ALL])

DOCUMENT 80 of 85:

AI: AUTHOR

Ernstrom H; Magiste K; Plantin LG; Fonnun F; Hedstrom KB;
Theodorsson-Norheim E; Christensson K; Stalberg E; Heilbronn E

TI: TITLE

Effects of manganese oxide on monkeys as revealed by a combined
neurochemical, histological and neurophysiological evaluation.

SO: SOURCE

Arch Toxicol; VOL 61, ISS 1, 1987, P46-52

PY: PUBLICATION YEAR

1987

LA: LANGUAGE

English

AB: ABSTRACT

Four monkeys were exposed to a total of 8 g each of manganese as oxide by repetitive subcutaneous injections during 5 months, after which they were left for 1 week to 6 months before they were sacrificed. All animals developed hyperactive behaviour after about 2 months. About 5 months after the start of the exposure the animals became hypoactive with an unsteady gait, and subsequently an action tremor appeared in some of the animals. The animals lost power in both upper and lower limbs and the movements of the hands and feet were very clumsy. The serum content of manganese rose 10-40 times during the exposure time and the content in brain was generally increased more than 10 times, with the highest content found in globus pallidus and putamen. The observed neurochemical effects were also largest in globus pallidus and putamen. In these regions there was a considerable depletion of dopamine and 3,4-dihydroxyphenylacetic-acid, while the homovanillic acid content remained almost unchanged. A severe neuronal cell loss was observed in globus pallidus but not in other regions. This is in accordance with results from the most recent neuropathological study of a human suffering from chronic manganese poisoning [Yamada et al. (1986) Acta Neuropathol 70: 273-278] where globus pallidus was devoid of neuronal cells while the content of pigmented cells in substantia nigra was normal. Our data suggest a reduction in number of dopaminergic nerve terminals, as the activity of the dopamine synthesizing enzyme DOPA-decarboxylase was also lowered. (ABSTRACT TRUNCATED AT 250 WORDS) ABSTRACT.

Output generated from Compact Cambridge: POLTOX 1987 - March 1990

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MANGANESE(ALL) OR MN(ALL) AND (NEUROTOX(ALL) OR NEUROTRANSMIT(ALL) OR
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NERVOUS(ALL)) AND MANGANESE(ALL)

DOCUMENT 55 of 85:

AA: AUTHOR

Roels H; Lauwerys R; Buchet J-P; Genet P; Garhan MJ; Hanotiau I; de Fays M;
Bernard A; Stancescu D

TI: TITLE

Epidemiological Survey Among Workers Exposed to Manganese: Effects on Lung,
Central Nervous System, and Some Biological Indices

SO: SOURCE

American Journal of Industrial Medicine, Vol. 11, No. 3, pages 307-327, 56
references, 1987

FY: PUBLICATION YEAR

1987

LA: LANGUAGE

English

AB: ABSTRACT

An epidemiological survey was conducted to evaluate the effects of exposure to manganese (7439965) on the lung, central nervous system, and selected physiological parameters of industrial workers. A group of 141 male workers exposed to manganese formed the experimental group and were compared to 104 comparison subjects. Relative to the comparison group, the exposed group exhibited an increased tendency towards developing coughs in the winter, dyspnea during exercise, and incidences of acute bronchitis. The lung function parameters such as forced vital capacity, peak expiratory flow rate, and others were only mildly changed in exposed workers who were also either previous or current smokers. Smoking and manganese exposure showed no synergy, nor were the changes in smokers related to manganese levels in blood or urine. There was a small increase in the prevalence of fatigue, irritability, tinnitus and trembling of fingers in the exposed workers. Exposure to manganese had significant adverse effects on audio verbal short term memory capacity, eye hand coordination, reaction time and steadiness of the hand. The manganese group also had altered serum levels of ferritin, calcium, copper, and ceruloplasmin. Exposed workers had an increased number of circulating neutrophils. Changes in these biological and neurological parameters were not related to exposure levels in a dose dependent fashion. Hand tremors, eye hand coordination and blood calcium levels were related to manganese levels in blood. The authors conclude that a time weighted average exposure to manganese dust at 1mg/m3 for less than 20 years may result in preclinical signs of intoxication. ABSTRACT.

8F: TOXIC

TI: Chronic manganese poisoning: a neuropathological study with determination of manganese distribution in the brain.

AU: Yamada-M; Ohno-S; Okayasu-I; Ikeda-R; Hatakeyama-S; Watanabe-H; Ushio-K; Tsubokoshi-H

80: Acta-Neuropathol-Berl; VOL 70, 1986 3-4, 1986, P273-8

85: An autopsy case of a 52-year-old man suffering from chronic manganese poisoning (CMP) is reported with determination of the manganese distribution in the brain. The patient had been working in a manganese ore crushing plant since 1965. In 1967 he began to complain of difficulties in walking and diminished libido. Later, he developed various neuropsychiatric symptoms including euphoria, emotional incontinence, masked face, monotonous speech, "cock-walk", increased muscle tone, weakness of upper and lower extremities, tremor of the eye lids, and exaggeration of knee jerks. The major neuropathological change was degeneration of the basal ganglia, in which the pallidum was severely affected. The pallidum disclosed a loss and degeneration of nerve cells, which was especially marked in the medial segment, a prominent decrease of myelinated fibers, and moderate astrocytic proliferation. The substantia nigra was intact. Distribution of manganese in the brain of the present case of CMP was determined using flameless atomic absorption spectrometry and compared with control cases and also a case of Parkinson's disease (PD). There was no significant difference between the control cases and the case of PD in average concentration of manganese and its distribution in the brain. The present case of CMP showed no elevation in average concentration of manganese in the brain. However, there were some changes in its distribution. Thus, the continuance of neurological disorders in CMP is not linked to an elevated manganese concentration itself in the brain. CMP appears to be different from PD in neuropathology and manganese behavior in brain.

AN: 87022052

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TOXLINE (R) 1981 - 1987

28 of 118

SF: ETIC
 TI: BRAIN MANGANESE, CATECHOLAMINE TURNOVER, AND THE DEVELOPMENT OF STARTLE IN
 RATS PRENATALLY EXPOSED TO MANGANESE
 AU: MONTUR-PJ; FECHTER-LD
 SO: TERATOLOGY; 32:1-11,1985
 AB: ETIC/ORNL
 AN: 85037574

31 of 118

SF: TOXBIE
 TI: Effect of low protein diet on manganese neurotoxicity: III. Brain
 neurotransmitter levels.
 AU: Ali-MM; Murthy-RC; Mandal-SK; Chandra-SV
 SO: Neurobehav-Toxicol-Teratol; VOL 7, ISS 5, 1985, P427-31
 AB: The effect of concurrent low protein (10% casein) diet and manganese (Mn)
 exposure (3 mg/ml drinking water) on brain levels of dopamine (DA),
 norepinephrine (NE) and 5-hydroxytryptamine (5-HT) were investigated in
 Fo-growing (90 days exposure), Fo-diet rehabilitated (low----normal protein
 diet-28 days) and F1-weaned rats. Mn exposure in either diet group resulted in
 a significant increase in the DA and NE levels but a decrease in the 5-HT
 level. These effects were more pronounced in the rats fed the low protein
 diet, especially in the F1-offsprings. Diet rehabilitation reduced the effects
 of Mn exposure.
 AN: 86092419

33 of 118

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PF: TMB15

TI: Biological aspects of occupational exposure to cadmium and several other metals

AU: Lauwerys-R; Buchet-JP; Roels-H; Bernard-A; Gennart-JP

SO: Rev-Epidemiol-Sante-Publique; VOL 34; ISS 4-5, 1986, P380-5

AB: We have performed several cross-sectional epidemiological surveys among workers exposed to cadmium, mercury vapour or **manganese** in order to assess : their early biological or functional effects; the biological tests allowing an assessment of the amount of metal absorbed or stored in the body; the acceptable exposure levels. Studies have also been carried out among persons exposed to inorganic arsenic in order to define its inactivation mechanism and to develop a biological test of exposure. The kidney is the main critical organ following long-term exposure to cadmium. To prevent the occurrence of renal changes in the majority of male workers exposed to cadmium, its concentration in renal cortex should not exceed 215 micrograms/g (wet weight); and that in urine : 10 micrograms/g creatinine. A blood cadmium level of 1 microgram/100 ml has been suggested as maximum tolerable level for long-term exposure. Prolonged exposure to mercury vapour may lead to renal and **neurological** disturbances. The preclinical signs of nephrotoxicity are correlated with the amount of mercury absorbed which may be assessed by monitoring the mercury level in urine. The **neurotoxic** effects (particularly tremor) are mainly related to the integrated exposure (duration and intensity). A maximal permissible level of 50 micrograms Hg/g urinary creatinine is proposed to prevent the occurrence of these toxic effects. An exposure to **manganese** dust for 7 years on the average at a level below the maximum allowable airborne concentration (5 mg/m³) recommended by the ACGIH in the USA may still lead to a slight reduction in psychomotor and spirometric performances and interfere with calcium metabolism. (ABSTRACT TRUNCATED AT 250 WORDS)

AN: 87148228

8F: TONBIS

18 of 118

TI: Effects of **manganese** chloride on the rat developing nervous system.

AB: Fristensson-K; Eriksson-H; Lundh-B; Plantin-LO; Wachtmeister-L; el-Azazi-M;

Morath-C; Heilbronn-E

SO: Acta-Pharmacol-Toxicol-Copenh; VOL 59, ISS 5, 1986, P345-8

AB: Sprague-Dawley rats were exposed to sublethal doses of **manganese** chloride during their postnatal development period up to 44 days of age. They showed transient clinical signs of disease and a decreased homovanillic acid (HVA) content in the striatum and hypothalamus between 15 and 22 days of age. The **manganese** content in the brain was increased 20-40 times during this period as determined with neutron activation analyses. In spite of this no structural damage or signs of maturation disturbances in the nervous system were found. Interruption of **manganese** exposure reversed the changes in HVA content.

AN: 87123569

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12 of 118

EF: NIOSH

TI: Manganese Absorption and Metabolism in Man

AU: Sandstrom-B; Davidsson-L; Cederblad-A; Eriksson-R; Lonnnerdal-B

SO: Acta Pharmacologica et Toxicologica, Vol. 59, Supplement VII, pages 60-62, 4 references, 1986

AB: The absorption and metabolism of **manganese** (7439965) was studied in healthy adults using a radioactive tracer. Fourteen health volunteers, ages 20 to 38 years, received either a test meal or a mineral solution containing labeled **manganese**. Whole body retention measurements with scintillators were made daily for the first 2 weeks and then weekly for up to 6 months. Two subjects were subsequently given intravenous injections of labeled **manganese** 6 months after oral administration and whole body retention was monitored in a similar manner. The biological half life of the radioisotope after oral administration was 13 ± 8 days for the first 20 days, and 34 ± 8 days for days 20 through 50. In the two subjects that received **manganese** both orally and intravenously, the biological half lives for the first 20 days after oral administration were 8 and 15 days, and 23 and 65 days, respectively, after intravenous administration. **Manganese** absorption was measured after oral intake of 450 milliliters of cow's milk baby formula containing 50 micrograms per liter **manganese**, or a multielemental preparation containing 2.5 milligrams **manganese**. The absorption of **manganese** from the infant formula was 8.4 ± 4.7 percent, with the exception of one subject with iron deficiency anemia, in whom 45.5 percent of the **manganese** was absorbed. Absorption from the multielemental preparation was 8.9 ± 3.2 percent. The authors conclude that the metabolism of **manganese** is dependent on the route of administration and

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ries greatly between individuals. The authors further conclude that iron deficiency anemia substantially increases **manganese** absorption and may increase the risk of **manganese** toxicity.

AN: 00166706

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SF: NIOSH

TI: Behavioral Effects of Chronic Manganese Administration in Rats: Locomotor Activity Studies

AU: Nachtman-JP; Tubben-RE; Commissaris-RL

SO: Neurobehavioral Toxicology and Teratology, Vol. 8, No. 6, pages 711-715, 1986, references, 1986.

AB: The effects of chronic administration of manganese (7439965) (Mn) on behavior in rats were tested using a measure of locomotor activity. Male Sprague-Dawley-rats were provided with drinking water containing 0 or 1mg/ml of manganese-chloride (7773015) ($MnCl_2$). Mn did not affect body weights. After 14, 29, 41, and 65 weeks, the locomotor stimulant effects of administration of d-amphetamine (300629) were determined. Locomotor activity was increased in Mn treated rats at weeks five, six, and seven, but subsequently returning to control levels. Activity levels were higher in Mn treated animals. Mn treatment had no effect on habituation. By week 13 there was no Mn effect. d-Amphetamine significantly increased activity, and the observed interaction effect indicated greater stimulating effect of d-amphetamine in Mn treated animals. At weeks 41 and 65, there was no difference in the responsiveness of the two groups to the stimulant effects of d-amphetamine. The authors conclude that oral exposure of rats to a low dose of Mn resulted in a transient increase in both basal and d-amphetamine stimulated activity. These effects may represent an animal model for the "manganese madness" phase of Mn toxicity in humans.

AN: 00166953

2F: TOXIC

TI: Effect of low protein diet on manganese neurotoxicity: I. Developmental and biochemical changes.

AU: Ali-MM; Murthy-RD; Saxena-DK; Srivastava-RS; Chandra-BV

SO: Neurobehav-Toxicol-Teratol; VOL.5, 188 3, 1983, P377-83

AB: The first in a series of studies on the effect of concurrent low protein diet (16% casein) and manganese exposure (Mn^{2+} , 3 mg/ml drinking water) in rats is reported here. The effect on growing (Fo-90 days) rehabilitated (Fo low leads to normal protein diet-28 days) and the F1 generation pups (weaned) were studied. Mn^{2+} exposure had no significant effect on growth pattern, brain weight or brain and plasma protein contents in either dietary groups. The diet regimen had no significant effect on the accumulation of Mn^{2+} in brain in any of the groups studied but the levels were higher in the F1 pups than in the parent (Fo) generation. In the F1 pups Mn^{2+} exposure had no effect on eye opening in either dietary group, delayed the development of startle reflex in low protein fed group only but the air righting reflex development was delayed in both the dietary groups, the effect being more marked in the low protein fed group. These changes reflect the early neurotoxic effect of Mn^{2+} .

MESH: Animal-; Blood-Proteins-metabolism; Brain-metabolism; Female-; Male-; Nerve-Tissue-Proteins-metabolism; Organ-Weight-drug-effects; Protein-Calorie-Malnutrition-metabolism; Rats-

MESH: *Brain-drug-effects; *Dietary-Proteins-pharmacology;

*Growth-drug-effects; *Manganese-toxicity;

*Protein-Calorie-Malnutrition-complications

AN: 83271721

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EF: NIOSH

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TI: The Effect Of Manganese Inhalation On Basal Ganglia Dopamine Concentrations In Rhesus Monkey

AU: Bird-ED; Anton-AH; Bullock-E

SO: Neurotoxicology, Vol. 5, No. 1, pages 59-66, 34 references, 1984

AB: The effect of **manganese** (7439965) inhalation on basal ganglia dopamine concentrations was studied in monkeys. Female rhesus-monkeys were exposed to 30 milligrams per cubic meter of **manganese-dioxide** (1313139) dust for 6 hours daily, 5 days a week, for 2 years. The animals were observed for clinical signs. After 2 years of exposure, the animals were killed and the brain was removed and dissected into the caudate, putamen, globus pallidus, and substantia nigra. Each brain part was assayed for dopamine and **manganese**. No abnormal behavior or neurological signs were noted in the monkeys during the exposure period. **Manganese-dioxide** caused a significant decrease in dopamine concentration in the caudate and globus pallidus. There was a slight, statistically insignificant decrease in dopamine concentration in the putamen. There was no difference in dopamine concentrations in the substantia nigra of the treated versus control animals. **Manganese-dioxide** caused a 60 to 80 percent increase in **manganese** concentration in all brain parts. The authors conclude that the dopamine system in the basal ganglia is susceptible to the effects of **manganese**. The amount of **manganese** inhaled and the length of exposure appear to determine whether abnormal neurological signs develop.

AN: 00141795

3F: N102H

47 of 118

TI: Differences In The Neurotoxic Effects Of Manganese During Development And Aging: Some Observations On Brain Regional Neurotransmitter And Non-Neurotransmitter Metabolism

40: Lai-JCK; Leung-TKO; Lim-L

30: NeuroToxicology, Vol. 5, No. 1, pages 37-47, 31 references, 1984

45: The effects of chronic manganese-chloride (7773015) exposure on neurochemical parameters were studied in rats. Wistar-rats were administered manganese-chloride-tetrahydrate (13446349) at a concentration of 1 milligram per milliliter (mg/ml) in their drinking water for periods ranging up to one lifespan, about 2 years. The animals were killed at selected intervals, their

brains were removed, dissected, and assayed for synaptosomal amine uptake, glutamic-acid-decarboxylase, choline-acetyltransferase, acetylcholinesterase (AChE), nicotinamide-adenine-dinucleotide (NAD) linked isocitric-dehydrogenase, and glucose-6-phosphate-dehydrogenase activities. Manganese-chloride caused transient, age dependent decrease in synaptosomal choline uptake in the hypothalamus and increases in uptake in the striatum. Synaptosomal noradrenaline and serotonin uptake were not affected. Manganese-chloride caused small decreases in choline-acetyltransferase activity in the cerebellum and midbrain after 2 months. The regional distribution of glutamic-acid-decarboxylase, AChE, or NAD linked isocitric-dehydrogenase in the brain was not affected. A 10mg/ml dose of manganese-chloride caused transient age dependent decreases in NAD linked isocitric-dehydrogenase activity, but had no effect on glucose-6-phosphate-dehydrogenase activities. In lifespan treatment with manganese-chloride, glutamic-acid-decarboxylase activity was decreased in the pons and medulla, choline-acetyltransferase activity was significantly increased in the cerebellum and cerebral cortex, and AChE activity was decreased in all brain parts. The authors conclude that encephalopathy induced by chronic manganese (7439965) poisoning affects brain development and aging in different ways. Lifespan treatment with manganese-chloride antagonizes age related decreases in NAD linked isocitric-dehydrogenase activities in most brain regions.

AN: 00142452

BF: NIOGH

TI: Neurotransmitters And Neurotransmitter Receptors In Developing And Adult
Rats During Manganese Poisoning

4U: Seth-PK; Chandra-SV

BD: NeuroToxicology, Vol. 5, No. 1, pages 67-76, 24 references, 1984

AB: The effects of manganese (7439965) (Mn) on neurotransmitters and neuroreceptors in the adult and developing rodent are reviewed. Clinical, neuropathological, and biochemical evidence is presented to show that central nervous system dysfunction during Mn toxicity is due to disturbances in the neurotransmitter system. Effects of Mn on monoamine concentrations in the brain of experimental animals are summarized and alterations in the metabolism of the neurotransmitter relative to variations in species, dose, and mode of Mn exposure are noted. The high affinity binding of appropriate agonists and antagonists of the neurotransmitter is described. Data is presented to show the inability of the neonate to metabolize Mn, and the effect of Mn exposure on dopamine concentrations and receptor sensitivity are reviewed. Neonatal exposure to Mn produces a decrease in binding of spiroperidol to striatal membranes and of serotonin (50679) to frontal cortical membranes. Studies are described that suggest the involvement of dopaminergic, serotonergic, cholinergic, and gamma-aminobutyric-acid functions in Mn neurotoxicity. The dopaminergic system is more sensitive since the activity of this receptor is altered only at low doses of Mn. The mechanism by which the concentration of monoamines is altered after Mn exposure is discussed.

AN: 00142523

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BF: N103H

TI: Effect Of Manganese Treatment On The Levels Of Neurotransmitters, Hormones, And Neuropeptides: Modulation By Stress

AC: Hong-J-B; Hung-C-R; Seth-PK; Mason-G; Bondy-SC

BC: Environmental Research. Vol. 34, No. 3, pages 242-249, 40 reference, 1984

AB: The neurochemical and endocrine effects of repeated injections of manganese were studied in rats. Male Fischer-344-rats were intraperitoneally injected with saline or 15 milligrams per kilogram manganese-chloride (7773015) daily for 6 weeks. A control group was not injected or handled. Rats were weighed and sacrificed 24 hours after the last injection. Various brain regions were analyzed for neurotransmitters and their acid metabolites and neuropeptides, and serum was analyzed for hormones. Compared to non injected controls, body weight was reduced 10 percent in saline controls and 30 percent in treated animals. Prolactin was increased 2.2 times and luteinizing hormone was decreased 65 to 75 percent in both saline and manganese injected animals, while testosterone was decreased 70 percent in the manganese group only. Corticosterone more than doubled in the saline controls but was not affected in the manganese group. Neuropeptide concentrations in the striatum and frontal cortex were not affected by any treatment. In the hypothalamus, both treated and saline control groups showed increases of 40 percent in beta endorphin, 20 to 30 percent in substance-P, and 20 percent in met-enkephalin. Pituitary neurotensin was increased 60 percent in the manganese group. Striatal concentrations of dopamine, dihydroxyphenylacetic-acid, homovanillic-acid, serotonin, and 5-hydroxyindoleacetic-acid were 25 to 40 percent greater in the manganese group than in non injected controls; saline control values were intermediate to those of the other groups. The authors suggest that manganese predominantly attacks the hypothalamic/pituitary axis. The interaction of neurotoxicant exposure and stress may serve to unmask toxic effects that would otherwise be imperceptible.

AN: 00144316

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AF: 012

TI: An epidemiological survey and clinical investigations on retired workers from **manganese** and ore grinders in Kyoto prefecture

AU: Sano-S; Yamashita-N; Kawanishi-S; Iguchi-H; Yoshinaga-T; Kojo-S; Tsukamoto-I; Fujita-H; Okamoto-H; Kato-N; et-al

SO: Journal of the Japanese Society for Hygiene June 1982, Vol.37, No.2, p.566-579. illus. 32 ref.

AB: Most of the 162 retired workers had been employed in small factories under poor working conditions. 55% of them had been exposed for more than 11 years. 46% had been in retirement for 11-20 years and 27% for more than 21 years. 124 unexposed people living in the same region served as the control group. The incidence of subjective symptoms associated with chronic **manganese** poisoning such as emotional instability, psychomotor irritability and **neurologic** abnormalities was high in the exposure group, increasing with the period of exposure to **manganese** dust. 28% reported subjective symptoms while they were still employed, but 45% of them reported as much as 6 years after their retirement. Of the retired workers, 5 (3.1%) had parkinsonism, 3 (1.9%) showed symptoms of hemiparkinsonism, and 15 (9.3%) showed **neurological** symptoms including mask-like face, unbalanced gait, slurred speech and impairment of fine movement. 39% of the retired workers were diagnosed as having pneum.

AN: 8301061

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TOXLINE (R) 1981 - 1987

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SF: TOXIC

TI: Histopathological alteration of the central nervous system in rats, following long-term administration of manganese chloride--relation to the activity of the brain tyrosine hydroxylase

AU: Nakashima-S

SO: No-To-Shinkei; VOL 35, ISS 1, 1983, P91-9

AB: Chronic manganese poisoning is characterized by mental and extrapyramidal disturbances. Parkinsonism-dementia complex (PD) on Guam is also manifested by progressive extrapyramidal syndrome and dementia. In PD, the reduced activities of catecholamine synthesizing enzymes in the brain has been demonstrated. On the other hand, the soil and water in Guam are rich in manganese, and one of the possible etiologic factors is trace element dysmetabolism in PD. The purpose of this paper is to clarify the effect of chronic manganese loading on the central nervous system. Manganese chloride (10 mg/ml of demineralized and distilled water) was administered orally to Wistar female rats weighing 80-110 g. Six and 12 months after the administration, manganese loaded and control rats were sacrificed by perfusion for histological studies and by decapitation for the assay of tyrosine hydroxylase (TH) activity. The striatum, globus pallidus and substantia nigra were examined with electron microscopy. The brain for TH assay was dissected into four parts as the striatum, midbrain-thalamus, pons-medulla oblongata, and hypothalamus. Ultrastructural changes were overwhelmingly detected in the zona reticulata of the substantia nigra at 12 months. These changes were mainly composed of alterations of the postsynapse and neuronal soma--shrunk and electron dense dendrites accumulated degenerating materials and so-called simple atrophy-of-the-neuron. Alterations in the presynapse were extremely milder than those in the postsynapse and neuron. At both 6 and 12 months, no significant changes in the striatum and globus pallidus were detected except for irregular windings of the plasma membrane in the axon terminal of the globus pallidus at 12 months. (ABSTRACT TRUNCATED AT 250 WORDS)

AN: 84080174

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6P: TOXIC

II: Effect of low protein diet on manganese neurotoxicity: II. Brain GABA and seizure susceptibility.

AB: Ali-MM; Murthy-RC; Saxena-DK; Chandra-SV

SD: Neurobehav-Toxicol-Teratol: VOL 5, ISS 3, 1983, P385-9

AB: The effect of manganese (Mn^{2+} , 3 mg/ml-drinking water) on brain GABA content and electroshock seizure susceptibility in low (10% casein) and normal (21% casein) protein fed rats were investigated. Manganese exposure caused a decrease in the brain GABA content, lowered the seizure threshold and increased the seizure duration. These effects were more marked in the low protein fed rats. Diet rehabilitation caused a recovery in the GABA levels but has only a moderating effect on the seizure susceptibility and duration. An inverse correlation was observed between the brain GABA levels and seizure threshold. Results indicate a lowered GABA-ergic activity and a functional dysbalance between the GABA-ergic-dopaminergic neuronal systems in manganese toxicity.

AN: 83271722

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SF: NIOSH

TI: Manganese Neurotoxicity: A Model For Free-Radical Mediated

Neurodegeneration

AU: Donaldson-J; McGregor-D; LaBella-F

SO: Canadian Journal of Physiology and Pharmacology, Vol. 60, No. 11, pages 1395-1405, 46 references, 1982

AB: Some effects of **manganese** (16397914) on the central nervous system were investigated in rats. Neonatal Sprague-Dawley-rats received daily injections of a control saline solution or 20 micrograms per gram body weight **manganese-chloride** (7773015) for 14 days. Rats were then killed and brains removed. The effects of **manganese** on central nervous system lipid peroxidation were observed through the malondialdehyde (542789) produced as an indicator of free radical activity. Individual regions of the brain were studied. Other male Sprague-Dawley-rats were injected intracerebroventricularly with saline or 25 micrograms **manganese-chloride**. At 1 hour animals were killed and the norepinephrine contents determined. There was considerable variation in the lipid peroxidation in various brain regions of newborn rats. High activity was found in the cerebellum and the hypothalamus, compared with the medulla oblongata and the midbrain. Treatment with **manganese** resulted in a drastic fall in lipid peroxidation which ranged from about 40 percent in the olfactory bulb to almost 100 percent in the striatum. The contents of norepinephrine fell significantly in the hypothalamus of **manganese** treated rats. The authors conclude that **manganese** reduces lipid peroxidation and the synthesis of norepinephrine in the rat brain.

AN: 00161236

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BF: NIOSH

TI: **Neurotoxic Effects Of Manganese: Studies On Cell Cultures, Tissue Homogenates And Intact Animals**

AU: Heilbronn-E; Eriksson-H; Haggblad-J

SO: **Neurobehavioral Toxicology and Teratology**, Vol. 4, No. 6, pages 655-658, 27 references, 1982

AB: Studies on the effects of **manganese** (7439965) on neonatal and adult rats during chronic and acute exposure are reviewed. In early animal experiments, 3 day old rats intubated with 75 to 150 milligrams (mg) labeled **manganese** over several weeks were slow in gaining weight compared with controls. Brains of newborn animals took up considerably more **manganese** than did those of older animals. A study on the localization of **manganese** is discussed. Uptake from the gastrointestinal tract is slow, but the brain accumulates **manganese** in certain areas faster than in others. A study of rats after 30 days of exposure to **manganese** found the brain accumulation to be highest in the striatum, followed by the midbrain, thalamus, olfactory bulb, and cerebellum. The high percentage increase found in the corpus callosum suggests an affinity of **manganese** for myelinated fibers. Preliminary behavioral test results correlated to transmitter studies on live animals indicate increased motor activity in rats after several weeks of daily exposure to 150mg **manganese-chloride** (7773015). Increased contents of gamma-aminobutyric-acid (56122) in the striatum of rats exposed to **manganese** for 2 months have been observed. **Manganese** has the ability to be involved in several reduction/oxidation reactions. **Manganese** was found to inhibit lipid peroxidation when performed on adrenergic and cholinergic neuroblastoma cells in culture. In human studies, severe symptoms include those for **manganese** madness and those similar to Parkinsonism. Late peripheral nerve lesions from **manganese** have also been described. Other studies suggest that **manganese** displaces certain other ions present in the brain. The authors conclude that the central catecholaminergic system is attacked by **manganese** compounds.

AN: 00145058

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Dr: NIDDM

TI: Alterations In Brain Dopamine And GABA Following Inorganic Or Organic Manganese Administration

AL: Granatados-G; Murray-MT

SO: Neurotoxicology, Vol. 3, No. 3, pages 75-82, 34 references, 1982

AB: The effects of manganese-chloride (7773015) (MnCl₂) and methylcyclopentadienyl-manganese-tricarbonyl (12108133) (MMT) on brain dopamine (DA) and gamma-aminobutyric-acid (GABA) were investigated in male CD-1 mice. Mice received 4 percent MnCl₂ in diets for 6 months or MMT subcutaneously at 10, 20, and 80 milligrams per kilogram (mg/kg) on alternate days for 3 weeks. Controls received subcutaneous injections of propylene-glycol. After treatment mice were killed and brain GABA was assayed. DA and choline-acetyltransferase (CAT) were measured. MnCl₂ administered in the feed reduced brain DA concentrations significantly. The DA of striatum nigra and olfactory tubercles were reduced by 21.5 and 18 percent, respectively, compared with controls. No changes were seen after 1 or 2 months. MMT injected at 20 and 80mg/kg reduced striatal DA by 10 and 23 percent, respectively. The olfactory tubercle was more resistant to the DA depleting effects of MMT. MnCl₂ elevated concentrations of GABA in striatum and

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stantia nigra, while MMT produced a similar effect but only at 80mg/kg dose. The cerebellum concentration of GABA was not affected by either compound. Acute injection of MMT failed to alter GABA concentrations in the brain. CAT remained unchanged in all regions of the brain after MnCl₂ treatment, suggesting that cholinergic neurons were spared the neurotoxic effects of manganese. The authors conclude that long term treatments with MnCl₂ and MMT induce changes in neurotransmitter concentrations.

AN: 00140115

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Output generated from Compact Cambridge: POLTOX 1987 - March 1990

Search Strategy:

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(NEUROLOG[ALL] OR NEUROPATH[ALL]) OR (NERVE[ALL] OR NERVES[ALL] OR
NERVOUS[ALL])) AND MANGANESE[ALL]

DOCUMENT 41 of 55:

AD: AUTHOR

Eriksson H; Magiste K; Plantin L-G; Fonnun F; Hedstrom K-G;
Theodorsson-Norheim E; Kristensson K; Stalberg E; Heilbronn E

TI: TITLE

Effects of Manganese Oxide on Monkeys as Revealed by a Combined
Neurochemical, Histological and Neurophysiological Evaluation

SO: SOURCE

Archives of Toxicology, Vol. 61, No. 1, pages 46-52, 41 references, 1987

PY: PUBLICATION YEAR

1987

LA: LANGUAGE

English

AB: ABSTRACT

The neurochemical, neurophysiological, and histological effects of high doses of manganese-oxide (1317357) were studied in monkeys. Manganese-oxide was administered by subcutaneous injection in a suspension of olive-oil. The animals received a total of 8 grams of manganese (7439965) over 5 months. Evaluation parameters included animal behavior as recorded on videotape, manganese levels in various brain areas, monoamine analysis, enzymatic activities of DOPA-decarboxylase (DDC), choline-acetyltransferase (CAT), and glutamic-acid-decarboxylase (GAD), glutathione analysis, and needle electromyographic analysis of the tibial anterior and quadriceps femoris muscles after stimulation of the peroneal nerve. Behavioral changes included established hyperactivity after 2 months and hypoactivity after 5 months. Motor weakness, tremor, and myoclonus were observed during the later stages. Exposed monkeys showed significant losses of neurons and concomitant astrogliosis in the pallidum. Blood manganese levels were approximately 20 times the control values throughout the experiment, and different brain regions showed different susceptibilities to manganese uptake. The highest levels of brain manganese were reported in the globus pallidus, caudate nucleus, substantia nigra, cerebral cortex, and cerebellum, and significant reductions of dopaminergic and serotonergic chemicals were observed in these areas. The activities of DDC and CAT were reduced in the putamen and globus pallidus, and the activity of GAD appeared unaffected by the treatment. Brain glutathione levels were depressed in the manganese exposed animals. There was no evidence of peripheral neuropathy or disturbed neuromuscular transmission. ABSTRACT.

Output generated from Compact Cambridge: POLTOX 1987 - March 1990.

Search Strategy:

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(NEUROLOG[ALL] OR NEURIPATH[ALL]) OR NERVE[ALL] OR NERVE[ALL] OR
NERVOUS[ALL]) AND MANGANESE[ALL]

DOCUMENT 10 of 85:

SI: AUTHOR

Cox DM; Traiger GJ; Jacober BP; Hanzlik RF

TI: TITLE

Comparison of the Toxicity of Methylcyclopentadienyl Manganese Tricarbonyl
with that of its Two Major Metabolites

SO: SOURCE

Toxicology Letters, Vol. 39, No. 1, pages 1-5, 9 references, 1987

PY: PUBLICATION YEAR

1987

LA: LANGUAGE

English

AB: ABSTRACT

Pneumotoxicity and lethality resulting from administration of methylcyclopentadienyl-manganese-tricarbonyl (12108133) (MMT) and its two major metabolites, hydroxymethylcyclopentadienyl-manganese-tricarbonyl (CMT-CH₂OH) and carboxycyclopentadienyl-manganese-tricarbonyl (12082074) (CMT-COOH), were compared in Sprague-Dawley-rats. Each dose of each compound was administered to a group of four rats which were then observed for 14 days. MMT was administered by intraperitoneal (ip) injection of single doses of between 6.0 and 37.4mg/kg. At all doses except the lowest, significant tonic clonic convulsive activity was observed, and mortality usually occurred within 15 minutes of dosing. The 50 percent lethal dose of MMT was calculated to be 12.1mg/kg. Extensive mottling, hemorrhage and distention of the lungs were observed on gross pathological evaluation. Neither CMT-CH₂OH, administered ip at doses of between 100 and 400mg/kg, nor CMT-COOH, administered ip at a dose of 250mg/kg, resulted in significant toxicity except at the highest dose of CMT-CH₂OH. In this case, two of the animals experienced convulsions and died. The authors conclude that MMT is much more toxic than either of its two metabolites. They suggest that the differences in toxicity may be due to changes in solubility of the metabolites allowing for decreased distribution into the central nervous system and a more rapid excretion rate. They conclude that the oxidative metabolism of MMT is an important detoxifying pathway. ABSTRACT.

8F: TOKSIS

II: Fertility of male workers exposed to mercury vapor or to **manganese** dust: a questionnaire study.

AU: Lauverys-R; Roels-H; Genet-P; Toussaint-G; Bouckaert-A; De-Cocman-2

80: Am-J-Ind-Med: VOL 7, 188 1. 1985, F171-2

AB: The fertility of male workers exposed to mercury vapor or to **manganese** dust was assessed with the use of the questionnaire developed by Levine et al (1960). In the mercury group (concentration of mercury in urine ranging from 5.1 to 172.1 micrograms/g creatinine), no statistically significant difference was found between the observed number of children and that expected on the basis of the reproductive experience of a well-matched control group. On the contrary, by comparison with their corresponding controls, the **manganese-exposed** workers exhibited a statistically significant deficit in the number of children during their period of exposure to the metal. The airborne concentration of **manganese** dusts at the different workplaces ranged from 0.07 to 8.61 mg/m³ with a geometric mean of 0.94 mg/m³.

AN: 85145863

SP: N102H

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TI: Chronic Manganese Poisoning: A Neuropathological Study with Determination of Manganese Distribution in the Brain

AU: Yamada-M; Ohno-S; Okayasu-I; Okeda-E; Hatakeyama-S; Watanabe-H; Ushio-K; Tsubagoshi-H

SO: Acta Neuropathologica, Vol. 70, No. 3-4, page 273-276, 27 references, 1986

AB: An autopsy case of chronic manganese (7439965) poisoning (CMP) was examined and the topographical distribution of manganese in the brain was determined. The patient had a history of occupational exposure to manganese for 12 years. Manganese was increased in the serum and urine. The major neuropathological change was degeneration of the basal ganglia, in which the pallidum, especially in its medial segment, was severely damaged. The substantia nigra was intact. There was no overall increase in manganese concentration in the brain. The manganese distribution did not show any significantly high value in the basal ganglia and cerebral white matter. Manganese concentration was increased in the gray matter of the cerebral cortex and decreased in the basal ganglia. The authors conclude that the continuance of neurological disorders in CMP is not linked to elevation of manganese concentration itself in the brain. They also suggest that chelation therapy might possibly be effective only in the early phase of CMP, during which the brain damage would be reversible.

AN: 00163957

SilverPlatter 1.6

TOXLINE (R) 1981 - 1987

41 of 118

EF: M102H

TI: The Effects Of Manganese On The Cholinergic Receptor In Vivo And In Vitro
May Be Mediated Through Modulation Of Free Radicals

AD: Donaldson-J; LaBella-FB

SO: NeuroToxicology, Vol. 5, No. 1, pages 105-112, 30 references, 1984

AB: The effects of manganese (7439965) on the central nervous receptor were studied in-vitro and in-vivo in rats. Whole rat brain homogenates were incubated in a medium containing dopamine, manganese-chloride (7773015), and tritium (H-3) labelled 3-quinuclidinyl-benzilate (QNB). Following incubation, the mixture was assayed for QNB binding to the brain cells by determining H-3 activity. Neonatal rats of unspecified strain were injected subcutaneously with 20 micrograms per gram manganese-chloride daily for 14 days. The rats were then killed and their brains were removed, dissected into various parts, and assayed for QNB binding. Brain homogenates were prepared and assayed for lipid peroxidation. In-vitro QNB binding in rat brain homogenates was reduced by manganese-chloride. Manganese caused a significant increase in QNB binding in striatal tissue of neonatal rats. No effect was seen in other brain regions. Lipid peroxidation was significantly reduced in all brain regions of neonatal rats. The authors conclude that manganese can act either as an oxidant or a powerful antioxidant in rat brains. Which role manganese takes may depend on the redox status of a particular brain region as well as on the amount of manganese deposited there.

AN: 00142077

3F: ETIC

TI: EFFECT OF MANGANESE CHLORIDE INTOXICATION ON GAMMA-AMINOBUTYRIC ACID LEVEL AND SYNTHESIS IN THE RAT BRAIN DURING PREGNANCY AND LACTATION

AU: KOSICKA-B; KITTEL-M; SMIALEK-M

SO: NEUROPATHOL POL; 23:201-209, 1985

AB: ETIC/GRNL

AN: 85042222

34 of 118

2F: NIOSH

TI: Brain Manganese Accumulation Following Systemic Administration Of Different Forms

AU: Gianutsos-G; Seltzer-MD; Saymeh-R; Wang-Wu-M-L; Michel-RG

SO: Archives of Toxicology, Vol. 57, No. 4, pages 272-275, 11 reference, 1985

AB: Blood and brain accumulation of manganese (7439965) was studied in mice.

Male CD-1-mice were injected subcutaneously (sc) with manganese-dichloride (7773015), manganese-oxide (11129605), or methylcyclopentadienyl-manganese-tricarbonyl (12108133) in doses corresponding to 0.2 or 0.4 milliequivalent of manganese per kilogram (meq/kg). The mice were killed 2 hours to 21 days after injection. Blood and brain manganese concentrations were measured. Mice were given one to three weekly sc injections of 0.4meq/kg manganese as manganese-oxide or manganese-chloride. Blood and brain manganese concentrations were determined as before. Brain manganese concentrations were elevated to at least twice the control value 4 to 8 hours after administration, regardless of the chemical form of manganese injected. Blood manganese concentrations reached their maximum value 4 hours after injection of the oxide and remained elevated for 1 week. Blood manganese concentrations after manganese-chloride injection peaked at more than 10,000 percent of the control value within 1 hour and gradually declined over the course of 1 week; however, they were still 740 percent of the control value after 1 week. Peak brain concentrations occurred 24 hours after injection and remained elevated for at least 1 week. Repeated injections caused further increases in both brain and blood manganese concentrations. Elevated brain manganese concentrations after repeated injections decreased more slowly than after a single injection. Brain manganese concentrations after 21 days were comparable to those observed 1 week after a single

injection. The authors suggest that the slowly developing neurotoxicity in response to manganese exposure may be due to prolonged retention of manganese by the brain.

AN: 00154536

Output generated from Compact Cambridge: POLTOX 1987 - March 1990

Search Strategy:

MANGANESE[ALL] OR MN[ALL] AND ((NEUROTOX[ALL] OR NEUROTRANSMIT[ALL] OR
NEUROLOG[ALL] OR NEUROPATH[ALL] OR NERVE[ALL] OR NERVES[ALL] OR
NERVOUS[ALL]) AND MANGANESE[ALL])

DOCUMENT 81 of 85:

AD: AUTHOR

Fishman EE; McBainley PA; Gianutsos G

TI: TITLE

Neurotoxic effects of methylcyclopentadienyl manganese tricarbonyl (MMT) in the mouse: basis of MMT-induced seizure activity.

SO: SOURCE

Toxicology; VOL 45, ISS 2, 1987, P193-201

PY: PUBLICATION YEAR

1987

LA: LANGUAGE

English

AB: ABSTRACT

Methylcyclopentadienyl manganese tricarbonyl (MMT) is an organic manganese-containing compound which is used as an additive in unleaded gasoline. One neurotoxic effect of MMT in mice is seizure activity. In this study, seizures were observed in mice treated with MMT in propylene glycol or corn oil. The LD50 associated with seizure activity was lower in mice receiving MMT in propylene glycol (152 mg/kg) than in those receiving MMT in corn oil (999 mg/kg). Manganese concentrations in the brains of mice which showed seizure activity due to MMT were higher than in those that did not (2.45 micrograms/g vs. 1.14 micrograms/g for MMT treated in propylene glycol and 3.25 micrograms/g vs. 1.63 micrograms/g for MMT in corn oil). Mice treated with manganese chloride (MnCl2) showed increases in brain manganese comparable to those of the mice showing seizure activity due to MMT, but exhibited no sign of seizure activity. MMT in non-lethal seizure-inducing doses had no effect on the accumulation of 4-aminobutyric acid (GABA) in mouse brain. However, MMT inhibited the binding of t-[3H]t-butylbicycloorthobenzoate [3H]-TBOB (a ligand for the GABA-A-receptor linked chloride channel) in mouse brain membranes with an IC50 value of 22.8 microM. The data suggest that MMT (organic manganese) or a closely related metabolite and not elemental manganese itself is responsible for the seizure activity observed. The seizure activity may be the result of an inhibitory effect of MMT at the GABA-A receptor linked chloride channel. ABSTRACT.

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Search Strategy:

MANGANESE[ALL] OR MNI[ALL] AND ((NEUROTOX[ALL] OR NEUROTRANSMIT[ALL]) OR
NEUROLOG[ALL] OR NEUROPATH[ALL]) OR (NERVE[ALL] OR NERVES[ALL] OR
NERVOUS[ALL]) AND MANGANESE[ALL]

DOCUMENT 39 of 85:

AU: AUTHOR

Ferraz HB; Bertolucci PH; Pereira JS; Lima JG; Andrade LA

TI: TITLE

Chronic exposure to the fungicide maneb may produce symptoms and signs of
CNS manganese intoxication.

SO: SOURCE

Neurology; VOL 38, ISS 4, 1988, P550-3

PY: PUBLICATION YEAR

1988

LA: LANGUAGE

English

AB: ABSTRACT

Manganese (Mn) poisoning, a well-known hazard in miners and industrial workers, shares many features with Parkinson's disease. Two young agricultural workers with a parkinsonian syndrome, who mentioned exposure to the fungicide maneb (manganese ethylene-bis-dithiocarbamate), led us to investigate a new possible source of Mn intoxication. Fifty male rural workers with occupational exposure to maneb were compared with 19 rural workers without fungicide-exposure. We noted significantly higher prevalence of plastic rigidity with cogwheel phenomenon, headache, fatigue, nervousness, memory complaints, and sleepiness in the exposed group. In addition, we saw other neurologic signs, such as postural tremor, cerebellar signs, and bradykinesia, although without statistical significance. The data suggest that occupational exposure to pesticides containing Mn is a possible source of Mn intoxication of the CNS. ABSTRACT.

Output generated from Compact Cambridge: POLTOX 1987 - March 1990

Search Strategy:

((MANGANESE[ALL] OR MN[ALL]) AND ((NEUROTOX[ALL] OR NEUROTRANSMIT[ALL] OR
(NEUROLOG[ALL] OR NEUROPATH[ALL] OR NERVE[ALL] OR NERVES[ALL] OR
NERVOUS[ALL])) AND MANGANESE[ALL])

DOCUMENT 32 of 85:

AU: AUTHOR

Lipione JJ; Maines MD

TI: TITLE

Selective Vulnerability of Glutathione Metabolism and Cellular Defense
Mechanisms in Rat Striatum to Manganese

SO: SOURCE

Journal of Pharmacology and Experimental Therapeutics, Vol. 247, No. 1,
pages 156-161, 39 references, 1988

PY: PUBLICATION YEAR

1988

LA: LANGUAGE

English

AB: ABSTRACT

The effects of manganese (7439965) on whole brain and striatal glutathione (GSH) metabolism and cellular defense mechanisms were studied in rats. Adult male Sprague-Dawley-rats were administered 1750 micromoles per kilogram manganous-chloride (7773015) over a 7 day period by subcutaneously implanted osmotic minipumps. They were killed at the end of the dosing period, the brains were removed, and the striatum was dissected out. Whole brain and striatal homogenates and the mitochondrial, microsomal, and cytosolic fractions were prepared and assayed for catalase, glutathione-peroxidase (GSHPx), oxidized-glutathione-reductase (GSSG-red), gamma-glutamyl-transpeptidase (GGT), gamma-glutamylcysteine-synthetase (GGTcyase), GSH, dopamine, 3,4-dihydroxyphenylacetic-acid (DHPAA), 4-hydroxy-3-methylphenylacetic-acid (OHMePAA), and manganese.

Manganous-chloride significantly reduced the concentrations of dopamine, DHPAA, and OHMePAA in the striatum. The manganese contents of the mitochondrial fraction of the whole brain and striatum were significantly increased. Manganese significantly reduced whole brain and striatal cytosolic and mitochondrial GSHPx activity, the greatest reduction occurring in the striatal mitochondria. Catalase activity was decreased only in the striatum. Striatal GSH content was reduced sharply; however, whole brain GSH was reduced only slightly. Manganese increased whole brain and striatal GGT activity and decreased whole brain and striatal GSSG-red activity. The increases in GGT activity were similar in both the whole brain and striatum, whereas the decrease in GSSG-red was greater in the striatum. GGTcyase activity was not significantly affected by manganese. The authors conclude that the cellular defense mechanisms of certain enzymes important in GSH metabolism are significantly altered by manganese in the brain of rats, especially in the striatum. These changes may be involved in manganese neurotoxicity. ABSTRACT.

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NEUROLOG[ALL] OR NEUROPATH[ALL] OR NERVE[ALL] OR NERVES[ALL] OR
NERVOUS[ALL])) AND MANGANESE[ALL]

DOCUMENT 20 of 85:

AU: AUTHOR

Parenti M; Rusconi L; Cappabianca V; Parati EA; Groppetti A

TI: TITLE

Role of dopamine in manganese neurotoxicity.

SO: SOURCE

Brain Res; VOL 473, ISS 2, 1988, P236-40

PY: PUBLICATION YEAR

1988

LA: LANGUAGE

English

AB: ABSTRACT

Manganese chloride increased cell mortality when added to human fibroblast cultures. The toxicity of the metal was greatly enhanced by dopamine; this effect was antagonized by the presence in the culture medium of catalase and superoxide dismutase enzymes. Manganese chloride also caused a marked decrease of striatal dopamine concentrations when infused into rat substantia nigra. Manganese neurotoxicity was lowered by pretreating the animals with drugs that reduced striatal dopamine turnover rate. Administration of an antioxidant, such as vitamin E, also partially prevented striatal dopamine decline induced by intranigral manganese infusion. Therefore, the decreased availability or autooxidation of dopamine attenuated manganese neurotoxicity. These findings are in agreement with previous observations suggesting that manganese increases toxic products originating from dopamine catabolism. ABSTRACT.

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(MANGANESE[ALL] OR MN[ALL]) AND ((NEUROTOX[ALL] OR NEUROTRANSMIT[ALL]) OR
 (NEUROLOG[ALL] OR NEUROPATH[ALL]) OR (NERVE[ALL] OR NERVES[ALL] OR
 NERVOUS[ALL])) AND MANGANESE[ALL]

DOCUMENT 17 of 85:

AU: AUTHOR

Haug BA; Schoenle PW; Karch BJ; Bardos A; Holzgraefe M

TI: TITLE

Morvan's fibrillary chorea. A case with possible manganese poisoning.

SO: SOURCE

Clin Neurol Neurosurg; VOL 91, ISS 1, 1989, P53-9

PY: PUBLICATION YEAR
 1989

LA: LANGUAGE

English

AB: ABSTRACT

The clinical picture of Morvan's fibrillary chorea includes a. spontaneous muscular activity resulting from repetitive motor unit action potentials of peripheral origin (multiplets), b. autonomic dysregulation with profuse hyperhidrosis, and c. central nervous system involvement as shown by severe insomnia and hallucinosis. A case featuring all these symptoms is presented. Whereas known causative factors range from gold or mercury poisoning to autoimmune disorders, the presented case is the first one in which chronic manganese intoxication (occupational exposure) seems to be implicated. Manganese has been found to inhibit acetylcholine-esterase, and, as a consequence, may produce peripheral and central cholinergic hyperactivity.

ABSTRACT.

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NERVOUS[ALL]))

DOCUMENT 1 of 154:

AU: AUTHOR

Newland MC; Ceckler TL; Kordower JH; Weiss B

TI: TITLE

Visualizing manganese in the primate basal ganglia with magnetic resonance imaging.

SO: SOURCE

Exp Neurol; VOL 106, ISS 3, 1989, P251-8

PY: PUBLICATION YEAR

1989

LA: LANGUAGE

English

AB: ABSTRACT

The paramagnetism of manganese was exploited to obtain proton nuclear magnetic resonance (MR) images of manganese-rich tissue in the central nervous system in vivo. One *Macaca fascicularis* monkey inhaled $MnCl_2$ aerosol prior to imaging. A second *M. fascicularis* and two *Cebus apellas* were administered $MnCl_2$ in various doses intravenously. The monkeys' brains were imaged before and after manganese administration in coronal and horizontal planes that included the basal ganglia and substantia nigra. A T1-weighted pulse sequence exploited manganese's reduction of spin-lattice relaxation times and clearly distinguished several separate and specific regions after manganese administration: the caudate nucleus, the lenticular nuclei, the substantia nigra, a region corresponding to subthalamic nucleus and ventromedial hypothalamus, and the pituitary gland. The kinetics of manganese accumulation were important in determining the imaged intensity of these regions but the route of parenteral administration was not. Spin-lattice relaxation times showed that T1 was shortened at lower doses of manganese and remained shortened longer in the globus pallidus and pituitary gland while little effect appeared in gray and white matter. T1 effects in caudate and putamen effects were intermediate. These data suggest selective affinity for manganese in globus pallidus and pituitary. ABSTRACT.